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Development of a multinational clinical practice guideline: a practical structured procedure

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Abstract: INTRODUCTION: The development of a clinical guideline is a challenging process. National and international organizations have established a variety of approaches, grading systems, evaluation scales and voting modes, however a practical description which illustrates all steps from starting the initiative to publication and dissemination of the guideline is usually not provided. We describe a structured guideline procedure that can be adjusted to the requirements of other multinational guidelines. METHODS: Clinical scientists with experience of organizing and contributing to guidelines initiated this guideline project. A balance between scientific evidence and clinical experience was achieved by involving European specialist societies and physicians from 18 European countries. For persons contributing to the guideline process, different levels of involvement were defined. The tasks were assigned to different groups of persons, which formed scientific institutions. RESULTS: We describe organizational structures and institutions, a stepwise approach to tasks, and illustrate the multistep guideline development procedure in a flowchart diagram that shows the workflow and the assigned responsibilities and provides further details for the execution of each step, including timelines. The process is split into 4 phases: Foundation, Preparation, Voting and Publication. DISCUSSION: This structured procedure can serve as a blueprint for future multinational initiatives and may also aid future attempts to standardize and harmonize the guideline development processes. Although the described structured procedure is for a diagnostic guideline, it may also be appropriate for therapeutic guidelines by adjusting the acceptance criteria for statements and recommendations.

DOI: https://doi.org/10.1159/000511007

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-192834
Journal Article
Accepted Version

Originally published at:
Sonyi, Marc; Keller, Jutta; Fox, Mark; Hammer, Heinz F (2021). Development of a multinational clinical practice guideline: a practical structured procedure. Digestive Diseases, 39(5):477-487.
DOI: https://doi.org/10.1159/000511007

DEVELOPMENT OF A MULTINATIONAL CLINICAL PRACTICE GUIDELINE: A PRACTICAL STRUCTURED PROCEDURE

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Short Title: Structured guideline procedure

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Number of Tables: 0.

Number of Figures: 6.

Word count: 4.056 (240+3.816)

Keywords: Please provide 3–5 keywords highlighting the most important points of your paper.

Abstract

Introduction: The development of a clinical guideline is a challenging process. National and international organizations have established a variety of approaches, grading systems, evaluation scales and voting modes, however a practical description which illustrates all steps from starting the initiative to publication and dissemination of the guideline is usually not provided. We describe a structured guideline procedure that can be adjusted to the requirements of other guidelines.

Methods: Clinical scientists with experience of organizing and contributing to guidelines initiated this guideline project. A balance between scientific evidence and clinical experience was achieved by involving representatives of European specialist societies and physicians from 18 European countries. For persons contributing to the guideline process, different levels of involvement were defined. The tasks were assigned to different groups of persons, which formed scientific institutions.

Results: We describe organizational structures and institutions, a stepwise approach to tasks, and illustrate the multistep guideline development procedure in a flowchart diagram that shows the workflow and the assigned responsibilities and provides further details for the execution of each step, including timelines. The process is split into 4 phases: Foundation, Preparation, Voting and Publication.

Discussion: This structured procedure can serve as a blueprint for future initiatives and may also aid future attempts to standardize and harmonize the guideline development processes. Although the described structured procedure is for a diagnostic guideline, it may also be appropriate for therapeutic guidelines by adjusting the acceptance criteria for statements and recommendations.

Abbreviations

AGREE II: Appraisal of Guidelines & Evaluation II

BSGE: Bulgarian Society of Gastroenterology

CEBM: Centre for Evidence-Based Medicine

CG: Core Group

CGL: Core Group Leads

DELBI: Deutsches Leitlinien-Bewertungsinstrument

DGVS: Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten,

EAGEN: European Association for Gastroenterology, Endoscopy and Nutrition

ESNM: European Society of Neurogastroenterology and Motility

ESPGHAN: European Society for Pediatric Gastroenterology, Hepatology and Nutrition

HG: Heads of Guideline

GRADE: Grading of Recommendations Assessment, Development and Evaluation

GO: Guideline Office

MGT: Magyar Gasztroenterologiai Tarsasag

ÖGGH: Österreichische Gesellschaft für Gastroenterologie und Hepatologie

PICO: Population, Intervention, Comparison, Outcome

PPI: Patient and Public Involvement

Re: Reviewer

SIGE: Italian Society for Gastroenterology

SIGN: Scottish Intercollegiate Guideline Network

SRGH: Societatea Romana de Gastroenterologie si Hepatologie

Swiss NGM: Neurogastromotility Network

UEG: United European Gastroenterology

Introduction

Guidelines are an important tool for improvement and harmonization of clinical decision making that have the potential to improve patients' outcomes. (1) Guidelines may be classified as "evidence based", having been developed after a systematic research and evaluation of literature, such as the German S2e guidelines, or as "consensus based", having been developed by a representative group of experts using an structured consensus process, such as the German S2k guidelines. (2) Evidence based guidelines (3) may seem preferable because of higher scientific rigor, however they require a large base of scientifically sound and valid evidence. For clinically relevant topics for which such high quality evidence is not available consensus based guidelines (4) may serve to summarize current knowledge and harmonize clinical practice, and to set the agenda for future research.

For clinical practice guidelines, a consensus process is often used to evaluate and interpret the evidence in the context of the patient's and the doctor's values and preferences. (5,6) This can be a challenging process. National and international organizations have established a variety of different approaches, grading systems, evaluation scales and voting modes for the development of new guidelines, these include the AGREE II, DELBI, GRADE, SIGN, CEBM, Delphi Methods. (5–12). Recently, the Guidelines International Network identified 11 key components for guideline development, including composition of the guideline development group, decision making process, methods, evidence review and rating. (14) These recommendations are helpful on many levels; however, a practical description of these procedures illustrating all steps from starting the initiative to publication and dissemination of the guideline was not provided. In April 2019 the authors (HFH, MF, JK) initiated a multi-society / multinational *European guideline for indications, performance and clinical impact of H_2- and ^{13}C-breath tests in adult and pediatric patients*. By studying recent guidelines (15–19) and guided by the requirements set out by United European Gastroenterology (UEG) for grant support, a procedure which fitted the aims of this guideline was developed. Along the way challenges were encountered, plans were adapted, and a lot was learned about this process, including the pros and cons of different approaches and the timelines encountered.

This manuscript will share the experience that the authors learned during this process, with a focus on points that are generalizable to the development of other guidelines. A structured description of the guideline procedure is provided that can be adjusted to the requirements of other clinical practice guidelines. This blueprint may also aid future attempts to standardize and harmonize the guideline development processes.

Methods

The guideline project was initiated by clinical scientists with experience of the use of breath tests in clinical medicine and the research setting (20–31) and that have organized or contributed to other national and international guidelines. (19,32–43) A key aim was to provide a balance between the scientific evidence and the collective experience from experts working in medical systems in different European countries with a wide range of health-economic circumstances. To serve this purpose, the authors identified and obtained the endorsement of UEG member societies with a major interest in the topics of the guideline (EAGEN, ESNM and ESPGHAN), enlisted national societies representing different European regions (Austria, Bulgaria, Germany, Hungary, Italy, Switzerland, Romania and the United Kingdom) and collaborated with the UEG-Guideline initiative (44). In order to define and assign responsibilities throughout the guideline process the following scientific institutions where defined:

Heads of Guideline (HG): Three authors of this paper (HFH, MF, JK) initiated, obtained funding, coordinated, managed and supervised the guideline development process.

Core Group Leads (CGL): Seven experts (including the HG) were selected by the HG and / or nominated by scientific societies based on their experience and publications in the field. The CGL prepared a list of topics (main topics and subtopics) to be covered by the guideline. One of the CGL led each of the main topics. The CGL also defined the overall guideline process, grading system, evaluation scale and acceptance criteria and will lead the writing of the final manuscript.

Core Group (CG): 23 experts (including the CGL) were selected by the CGL and participating societies. The CG was composed of members from participating societies as well as experts with publications in the field and experience in guideline projects. Special consideration was given to representation of gender and age. The CG played a central role for the guideline development process. The key tasks were the development of statements and recommendations and their revision/modification after voting rounds as well as the review of drafts of the manuscript. For this purpose, the members of the CG were assigned, according to their personal interests, to specific topics of the guideline.

Reviewers (Re): Within a period of 3 months HG, CGL and CG recruited 22 professionals to serve as reviewers through calls to contributing societies and personal contacts. In total, 45 persons from 18 European countries were involved in the review process. Three rounds of a Delphi-voting process were planned with all those involved in the process encouraged to comment on statements and recommendations. Figure 1 shows the regional distribution of all participating persons.

Guideline Office (GO): The administrative work of the guideline office (MS, HFH) included management of the budget and costs related to work meetings, travel expenses and publications fees. In addition, it managed organizational matters including declarations of conflicts of interest and communication with supporting organizations. The GO was also responsible for literature search, information management, and preparation of voting, collection and consolidation of voting results and communication with all participants including regular updates.

Results

The development of a guideline is a multistep process. In order to illustrate the procedure in a comprehensible manner, we use a flowchart diagram that shows the workflow and the assigned responsibilities and provides further details for the execution. The *responsibility column* lists the involved institutions and indicates assignment of tasks with an "x". These institutions are Heads of Guideline (HG), Core Group Leads (CGL), Core Group (CG), Reviewers (Re) and Guideline Office (GO). The *workflow column* visualizes work steps (rectangles) and decision points (rhombus). An arrow represents tasks that are work in progress and executed parallel to other steps. Further explanations of each work step and decision point are provided in the *details column*. The procedure is split into 4 phases: Foundation, Preparation, Voting and Publication.

Phase 1: Foundation (Fig. 2a)

Phase 1 covered the foundation of the guideline development process from an organizational perspective. It comprised initiation of the development process, establishing basic requirements and formation of essential institutions. The development process started with an initiative of the HG, who discussed and **identified the need for a guideline**. The need for an updated guideline may be due to recent changes in knowledge or spread of application into uses or health care environments, which go beyond initially considered, specific clinical applications or health care environments. The key task of this step is review of literature and guidelines related to the topic, which is of fundamental importance for the justification of the whole process. After the idea for a new guideline was conceived, the HG needed to **identify stakeholders and interest groups** to back up the initiative. To provide the depth of knowledge and scientific expertise required, experts, characterized by important publications in the field, and / or position on the committees of international scientific societies were identified. Wide regional representation was achieved by involving local opinion leaders nominated by national societies. This ensured the guidelines were relevant to different clinical environments, clinical approaches and health-economic backgrounds with the aim to minimize disparities between health care systems across a large geographic area, which is a key aim of the UEG Guideline initiative that supported this project. At this stage, the HG also needed to secure **financing** of the guideline process. First, a budget with the expected cost for scientific staff and office personnel, work meetings, travel expenses and publication had to be developed. Subsequently the HG filed an application for a grant from UEG. Securing financing was completed by the end of phase 1 and was the prerequisite to advance to phase 2. Once finance was secured, HG **set up the Guideline Office** (GO) for administrative and scientific purposes. In cooperation with the Core Group Leads, the HG **established the Core Group** and assigned CGL to main topics of the guideline. A prespecified time schedule is a prerequisite for funding and for communication and cooperation with interest groups. Therefore, the HG and CGL **developed a timeline** using a Gantt Chart. However, flexibility of schedules was allowed in case of delays or developments. At this point Phase 1 was completed. The time course for the foundation phase of a guideline development process depends on various external factors that are not under control of HG - e.g. discussions with stakeholders and interest groups, securing financing - and therefore can vary considerably.

Phase 2: Preparation (Fig. 2b)

After completing the foundation phase and having laid the groundwork by establishing necessary institutions, the guideline development process entered phase 2, which focuses on preparation for the voting process. At the beginning of phase 2, the HG and CGL started with the **invitation of reviewers for the Delphi process**. Interested experts were identified and selected by participating interest groups, HG and CGL through personal contacts. Special attention was paid to a pan-European regional spread of reviewers as shown in Figure 1. After the invitation of reviewers had been initiated, the HG and CGL **defined the guideline process** in detail. This included specification of working structure and further procedure for the CG, definition of statements and recommendations including the grading system for recommendations and selection of voting mode with respective evaluation scale and acceptance criteria. The grading of recommendations was derived from the quality of evidence as assessed by Oxford Grading (11) and strength of recommendations was clarified by the wording used (Appendix Table 1). As for the voting mode, a three round Delphi process with digital voting sheets was selected. This facilitated the involvement of reviewers from all over Europe and allowed for voting to remain anonymous for all participants (details were known to GO), which was considered crucial to assure an unbiased and representative vote. For the assessment of agreement level, a 6-point Likert scale - reaching from “A+ agree strongly” to “D+ disagree strongly” - was used in the voting on statements and recommendations (Appendix Table 2). The acceptance criteria were defined as shown in Appendix Table 3. Statements and recommendations were accepted if they reached ≥80% of agreement (A+ or A) and <10% of disagreement (D+ or D) in Delphi voting. Next, the HG and CGL **defined topics for the guideline** by defining key questions to be answered by the guideline and by drawing up a list of main topics and subtopics to be covered by the guideline. As shown in Appendix Table 4, members of the CG were assigned to guideline topics according to their interests and the CGL were appointed to chair these topic groups. As the next step, the scientific GO **implemented the information management** for the process. Relevant publications for the development of statements and recommendations were identified by a systematic literature search (PICO) (45) and additional literature was collected from members of the CG. To facilitate information exchange and to allow easy access to the literature for all members of the guideline project, a cloud-based file sharing platform was set up. Members of the CG were enabled to upload and to read files, whereas reviewers were only permitted to read. Based on the identified literature, the CG and corresponding CGL developed **statements and recommendation**s for their respective topics. This included assigning strength to statements and recommendations, as well as provisional grading of recommendations in accordance with the predetermined definition. The final version of statements and recommendations of each main topic were sent to the scientific GO and were used to **prepare the Delphi process**. The GO collected and consolidated all proposed statements and recommendations and prepared spreadsheets for the Delphi voting. These spreadsheets included instructions on the voting process, the statements and recommendations with corresponding strength and grading, the 6-point Likert scale for evaluation and space for comments. An example of a spreadsheet for the Delphi voting is provided in Appendix Table 5. The time frame required for phase 2 was substantial, approximately 30 weeks.

Phase 3: Voting (Fig. 2c)

In phase 3, the Delphi voting took place. In total three Delphi rounds were conducted to reach a consensus on statements and recommendations. Hereinafter the first Delphi round is described in detail (representative of all three rounds). In addition, a detailed illustration of the voting process with focus on interactions between participating institutions is shown in the "swimlane" diagram in Figure 3. The **1st Delphi round** started with the GO sending out a mail with the spreadsheets for the Delphi voting to all reviewers. The spreadsheet contained instructions for the voting process and the request to response within a period of 3 weeks. Reviewers were asked to vote on statements and recommendations according to the predefined evaluation scale and to provide comments. Twice weekly updates about the progress of the voting process, supplemented towards the end of the 3-week period by "friendly reminders" of schedule were sent to the reviewers by e-Mail by the GO and HG to assure compliance with the deadline. This included a running total of the number of responses received. Completed forms were sent back by e-mail to the GO, which was responsible for the **collection of voting results**. All replies were consolidated by preparing a spreadsheet with all results and comments. Then the GO and HG defined five groups of statements and recommendations based on the predefined acceptance criteria:

a. "Accepted" according to the predefined criteria and no need for modification and further voting.
b. "Accepted" according to the predefined criteria with comments by reviewers which resulted in minor editorial modifications of the statement or recommendation by the GO and HG, not requiring revoting.
c. "Accepted" according to the predefined criteria with comments by reviewers which resulted in major modifications by the GO and HG requiring revoting in the next Delphi round.
d. "Not accepted" according to predefined criteria and considered to be likely by HG that a modification according to reviewers' comments may result in acceptance in the next Delphi round.
e. "Not accepted" and considered unlikely by HG that modifications will result in acceptance in the next Delphi round.

Statements and recommendations in groups a. and b. where consolidated in a separate spread sheet of "Accepted" with respective strengths, gradings and condensed voting results. Statements and recommendations in group e. were collected in a file "Not Accepted" with condensed voting results. These statements and recommendations will be reported in the final guideline manuscript as not having achieved consensus. Statements and recommendations in groups c. and d. where sent to the respective CGL with the request to modify them in cooperation with the members of their respective CG. These revised statements and recommendations entered the next Delphi round. This process took 6.5 weeks. Preparation and execution of the **next Delphi rounds** were performed in accordance to the 1st Delphi round. Due to the decreasing number of statements and recommendations that required voting, the 2nd and 3rd Delphi round only took 2 weeks each, with revision of statements after the 2nd Delphi round also taking 2 weeks. After each round, the GO **added the accepted**

statements and recommendations (a. and b. according to the list) to the spreadsheet “Accepted”. If after three Delphi rounds and revisions some statements and recommendations still were not accepted, they were added to group e.

Phase 4: Publication and Post-Publication (shown in Fig. 2d)

After completion of the Delphi voting, the project will enter the final stage of the development process: publication. The list of the **final statements and recommendations** for the new guideline will be sent to the HG and CGL for revision on grading in accordance to the predefined grading criteria. Following this, the HG and the CGL will prepare the manuscript for the guideline. Following publication of a clinical practice guideline the information shall be disseminated as widely as possible with the aim of improving medical care and identifying areas of research needs wherever these tests are applied. Dissemination may include translation into various European languages to facilitate local adoption, presentation at national and international meetings, classroom teaching and video clips on member society websites highlighting the key recommendations set out in the guidelines.

Discussion

Clinical Practice Guidelines assist physicians and provide them with the information required to deliver high quality care and / or to communicate the best care options to patients. (44) In a consensus process, the best available evidence is evaluated and interpreted in the context of the patient's and the doctor's values and preferences (5,6), taking account of local facilities and health care environments. The path to a new guideline can be challenging. Previous publications have recommended different approaches; (2,7–12) however, practical descriptions of guideline processes are lacking. This paper describes the structured procedure used to develop a multinational guideline. It is hoped that this can serve as a blueprint for future initiatives.

We describe organizational structures and institutions, a stepwise approach to tasks and the responsibilities assigned to contributors to the guideline process. In addition, time management is of great importance. Criteria for application for financial support usually require a description of the schedule of activities, for example using a Gantt chart. However, flexibility of timelines, especially in phase 2 of the guideline process (shown in Fig. 2b) is of fundamental importance for successful project management. Originally a duration of 14 weeks was scheduled for this step, whereas finally it took over 20 weeks. However, some of the additional time spent in phase 2 for the development and refinement of statements and recommendations and of grading of quality and strength was recovered in phase 3, when results of Delphi voting where better than expected and therefore decreased the time needed for rewording and preparation of the next Delphi round (and presumably also the time required for drafting the manuscript). Phase 3 was within the projected time course for which twice weekly updates and reminders of the reviewers we considered essential. Within the time span assigned for Delphi voting, the majority of responses were sent to the GO in the last days before the voting was closed. A total number of 167 statements and recommendations were sent to 45 reviewers in the 1st Delphi voting. During the 1st voting round we experienced a high rate of acceptance and the large majority of 138 statements and recommendations fulfilled the criteria. After revision and rephrasing, 28 statements or recommendations were voted on in a 2nd Delphi round, with 20 of these items meeting the acceptance criteria. Finally, there were only 6 statements and recommendations that required a 3rd Delphi round. During the process 17 statements were removed from voting and either moved to group e or were replaced by new statements or recommendations.

A key challenge in the development of any consensus-based guideline is to consider both the results of research studies (the evidence base) and a democratic vote representing diverse clinical practice and experience in a wide range of health care environments. Many aspects of clinical medicine have not been subjected to rigorous investigation. Established practice is not always evidence based and sometimes based on unproven assumptions. Indeed, with regards to breath testing, for example fructose breath testing, it can be argued that the evidence base is scarce and contradictory so that this test should not be performed at all. (46) However, some methods and some tests are so well established in clinical practice that this is not a position that can be accepted by the majority of practitioners and therefore these techniques should not be excluded from a consensus clinical guideline. It is important not to throw out the baby with the bathwater! A balance between the weight of evidence, the expertise of leading scientists, and the results of the Delphi voting process representing the opinions of experienced physicians working in different regions and in a wide range

of clinical circumstances has to be found. On this basis, to ensure that consensus was achieved, the CG considered it necessary to compromise, to accept that the majority position was not always "evidence based", find a level of agreement, and to formulate statements and recommendations that acknowledged the "absence of evidence" but provided clear guidance based on clinical experience. We consider that this approach is justified if it helps to ensure that guidelines are widely adopted and that tests are performed, analysed and interpreted to consistent standards. Incremental change to practice is the aim. Especially in version 1.0 of any guideline, it is essential that the opportunity is taken to discuss the evidence for and against current practice as outlined in the statements and recommendations. By highlighting where there is missing (or even contradictory) evidence, guidelines can set the agenda for future research, the results of which will inform the next iteration of the guideline.

Clearly the structured procedure outlined in this paper will not be appropriate for the development of all guidelines. The approach described here was for a diagnostic guideline. Although a similar approach may be appropriate for therapeutic guidelines, acceptance criteria for statements and recommendations are often higher in this setting, than the 80% threshold used in our Delphi process. Moreover, careful assessment of comments made by individual reviewers with modification of recommendations or statements can be constructive even if the minimum agreement level has been reached. This flexibility can help to achieve very high levels of consensus and ensure optimal uptake of recommendations in clinical practice.

One aspect of guideline development that is not covered in our structured approach to guideline development is Patient and Public Involvement (PPI). Successful guidelines that have a positive impact on clinical practice are generally simple, easy to apply and consistent with the values and preferences of those delivering and receiving medical care. Ideally patient representatives would be involved at every stage; however, this was not planned in this instance. Instead, after publication of the *European Guideline for indications, performance and clinical impact of H_2- and ^{13}C-breath tests in adult and pediatric patients* a qualitative and quantitative assessment of guideline adoption into clinical practice is planned. This will not only include feedback from doctors and other health care professionals but also from patients referred for breath test investigation. It is relatively easy to assess whether the guidelines are adopted and adhered to. However, publication of a new guideline also represents an opportunity to better understand the reasons why such tests are performed and also whether the expectations of all those involved are fulfilled by the investigation. This will inform the development of future breath test protocols and the next iteration of the guideline, with the aim that this technology will address ever more closely the needs and wants of doctors and their patients.

Statements

Acknowledgement (optional)

The authors are very grateful to the UEG and member societies (EAGEN, ESNM, ESPGHAN, BSGE, DGVS, MGT, ÖGGH, SIGE, SRGH, Swiss NGM) that supported and endorsed this activity. We are also very grateful to all members of the core group and the reviewers involved in the development of the *European guideline for indications, performance and clinical impact of H_2- and ^{13}C-breath tests in adult and pediatric patients*. Members of the core group in alphabetical order: Paul Afolabi, Guido Basilisco, Marc Benninga, Osvaldo Borelli, Enrique Dominguez-Munoz, Dan Dumitrascu, Mark Fox, Oliver Götze, Stephan Haas, Heinz Hammer, Johann Hammer, Bruno Hauser, Laszlo Herszenyi, Jutta Keller, Loris Lopetuso, Radislav Nakov, Daniel Pohl, Silvia Salvatore, Marc Sonyi, Teodora Surdea Blaga, Nikhil Thapar, and Kristin Verbeke. Name of Reviewers in alphabetical order: Istvan Altorjay, Giovanni Barbara, Franziska Baumann-Durchschein, Oana Belei, Stanislav Churchev, Maria Effenberger, Stefan Fürst, Antonio Gasbarrini, Karin Hammer, Zeljko Krznaric, Marcis Leja, Francois Mion, Agata Mulak, Ventsislav Nakov, Sieglinde Reinisch, Oleg Shvet, Magnus Simren, Radu Tatuian, Bojan Tepes, Hans Törnblom, Harald Vogelsang, Darija Vranesic Bender, and Clive Wilder-Smith.

Statement of Ethica: Not applicable

Disclosure Statement

MF has received research funding from Nestlé International for studies of lactose digestion and tolerance.
HFH is founder and owns shares of Carboception®

Funding Sources:

The guideline process was funded by a UEG Activity Grant for guideline development. The authors received no other funding from the public, commercial or not-for-profit sectors.

Author contributions

HH and MS led the guideline office, performed the literature search, collated the information and produced the first draft of the manuscript. JK and MRF contributed

393 additional material and edited the publication. All authors discussed and revised the draft
394 and approved the final version of the manuscript.
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Figure legends

Appendix: